

PCT

WORLD INTELLECTUAL PROPERTY  
International Bureau

REFERENCE BR

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: <b>A61K 31/43, 9/16, 47/20</b>		A1	(11) International Publication Number: <b>WO 95/25516</b> (43) International Publication Date: 28 September 1995 (28.09.95)
(21) International Application Number: PCT/EP95/01039 (22) International Filing Date: 20 March 1995 (20.03.95)  (30) Priority Data: 9405856.7 24 March 1994 (24.03.94) GB		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  Published <i>With international search report.</i>	
(71) Applicant ( <i>for all designated States except US</i> ): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).  (72) Inventor; and (75) Inventor/Applicant ( <i>for US only</i> ): HATTON, Anthony, Guy [GB/GB]; SmithKline Beecham Pharmaceuticals, Clarendon Road, Worthing, West Sussex BN14 8QH (GB).  (74) Agent: WALKER, Ralph, Francis; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).			
(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING BETA-LACTAM ANTIBIOTICS AND AN ALKYL SULPHATE SURFACTANT			
(57) Abstract  Pharmaceutical formulations, in particular beta-lactam antibiotic formulations in the form of substantially spherical granules, using a metal alkyl sulphate as a spheronizing agent.			

***FOR THE PURPOSES OF INFORMATION ONLY***

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Pharmaceutical formulations containing beta-lactam antibiotics and an alkyl sulphate surfactant ..

This invention relates to pharmaceutical formulations, in particular to beta-lactam antibiotic formulations in the form of substantially spherical granules.

- 5 In the manufacture of pharmaceutical formulations in which the active ingredient comprises a beta-lactam antibiotic and/or beta-lactamase inhibitor, it is frequently necessary to provide the formulation in the form of granules, for example for making up into tablets, capsules or sachet formulations etc. For certain applications in particular when such granules have to be coated, for example with a
- 10 water-resistant or enteric coating to delay dissolution after oral ingestion, it is desirable that the granules are substantially spherical.

The term "substantially spherical" as used herein is intended to include spherical, ellipsoidal, e.g. of eccentricity up to no more than 2, preferably up to no more than 1.5, oblate spheroidal, e.g. having its longest axes up to no more than 2 times, preferably up to no more than 1.5 times longer than its shortest axis, polyhedral with at least 12 faces having predominantly curved rather than angular edges, and substantially equiaxial. The term also includes the shape of what are known in the art as "marums". The terms "spheronised" and "spheronisation" are terms of the art.

- 20 It is particularly desirable to have substantially spherical granules when granules of relatively water soluble antibiotics, and of beta-lactamase inhibitors such as salts of clavulanic acid such as potassium clavulanate are to be coated, as the angles of angular granules can present weak points in the coat via which the antibiotic or inhibitor may be leached out. Problems have been encountered in
- 25 providing such antibiotics and beta-lactamase inhibitors in the form of granules, particularly in the form of substantially spherical granules.

According to this invention, there is provided a pharmaceutical granule, comprising:

- 30 an active ingredient which comprises one or more beta-lactam antibiotics and/or one or more beta-lactamase inhibitors; and one or more surfactants which are Group I or Group II metal ( $C_{10-17}$ ) alkyl sulphates.

The invention further provides a process for the preparation of a pharmaceutical granule, comprising admixing one or more beta-lactam antibiotics, and/or one or more beta-lactamase inhibitors with one or more surfactants which are Group I or Group II metal ( $C_{10-17}$ ) alkyl sulphates, and then granulating the mixture.

The granule is primarily intended for oral administration, and consequently preferred antibiotics are orally absorbed penicillins (which term

includes penicillins penems, penams, carbapenems etc.) or cephalosporins.

Preferred beta-lactam antibiotics are amoxycillin, for example as its trihydrate, and ampicillin. A preferred beta-lactamase inhibitor is a salt of clavulanic acid, especially group I metal salts thereof such as potassium clavulanate. A preferred

5 combination of beta-lactamase inhibitor and antibiotic is potassium clavulanate : amoxycillin, as amoxycillin trihydrate or sodium amoxycillin, for example as crystalline anhydrous sodium amoxycillin as described in EP 0131147. A preferred ratio of clavulanate : amoxycillin is in the range 1 : 1 to 1 : 12 inclusive, particularly 1 : 2 to 1 : 8, expressed in terms of weight ratios of the free acids.

10 Suitably the Group I or Group II metal alkyl sulphate has a formula  $[(C_nH_{2n+1})SO_4]_mM^m+$  where M is a group I or II metal cation of ionic charge m and n is an integer between 10 and 17. The surfactant(s) is preferably a sodium alkyl sulphate, for example sodium lauryl sulphate.

15 The granule may also comprise conventional granulating aids such as polyvinylpyrrolidone such as Kollidon K12-30 (Trade Mark) or the proprietary hydroxymethyl cellulose material "Pharmacoat 603" (Trade Mark), fillers / spheronising aids such as colloidal silica such as Aerosil 200 (Trade Mark) and/or cellulose derivatives such as microcrystalline cellulose, e.g. Avicel (Trade Mark).

20 When the granule comprises or contains a salt of clavulanic acid, e.g. potassium clavulanate either as the sole beta-lactamase inhibitor content or in admixture with other beta-lactamase inhibitors then it is preferred that the granule also contains an amino acid, suitably glycine.

25 The relative proportions of the above components in the granule are suitably as follows. Antibiotic, beta-lactamase inhibitors or combination thereof: 50 wt. % or more e.g. 80% or more. Surfactant: 0.5 - 5 wt. % e.g. 0.5 - 1.5 wt. %. Granulating aid: 0 - 7.5 wt. %, typically if the granule comprises or contains a salt of clavulanic acid as the sole or principal active ingredient content or in admixture with another antibiotic 3 - 7.5 wt. %, e.g. 4  $\pm$  1 wt. %. Fillers/spheronising aids 0 - 25 wt. % e.g. 0 - 10 wt. %. If an amino acid is present in the granule, for 30 example together with a salt of clavulanic acid, then suitably 1 - 50 wt. %, e.g. 5 - 15 wt. % may be present. These weight percentages are expressed as total granule weight.

The shape of the granules is preferably substantially spherical, as defined above, with a size range between 10-44 mesh, e.g. 12-30 mesh.

35 The invention further provides a process for the preparation of a pharmaceutical granule, comprising admixing one or more beta-lactam antibiotics, and/or one or more beta-lactamase inhibitors with one or more surfactants which

are Group I or Group II metal ( $C_{10-17}$ ) alkyl sulphates, and then granulating the mixture.

These granules may be prepared by a granulation process comprising for example mixing the milled ingredients with a suitable liquid, or by mixing the 5 milled ingredients less the granulating aid with a solution or suspension of the granulating aid, followed by extrusion and preferably spheronisation, e.g. "marumerisation". When the antibiotic comprises a relatively water-insoluble antibiotic such as amoxycillin trihydrate the suitable liquid may be an organic liquid or water, and when the antibiotic comprises a relatively water-soluble antibiotic 10 such as clavulanate a suitable liquid may be an organic liquid such as an isopropyl alcohol: methylene dichloride mixture, typically in a 1:2-3 volume: volume ratio.

Salts of clavulanic acid, such as potassium clavulanate are extremely water sensitive, so it is important that such salts are handled in extremely dry conditions, suitably 30% RH or less.

15 It has been found that spheronised granules, such as marums may conveniently be prepared using the above formulations and process.

The granules of this invention, especially substantially spherical granules, are suited to coating, for example with water-resistant or enteric coatings. This is particularly so in the case of granules of the invention in which the active 20 ingredient comprises or includes a salt of clavulanic acid.

Therefore the invention also provides a granule as described above, coated with a coating, which may be an at least partly water-resistant, suitably an enteric, coating.

25 The invention also provides a process wherein a granule as described above is coated with a coating, which may be an at least partly water-resistant, suitably an enteric, coating.

An enteric coating may for example be an essentially conventional enteric coating material known for coating antibiotic granules.

Suitable coating materials are pharmaceutically acceptable methacrylic 30 acid copolymers such as those described in the USP/NF, and such polymers of types A, B and C as described therein may be suitable. Suitable generic classes and specific examples of pharmaceutically acceptable methacrylic acid copolymer are known polymers which are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, for example having a molar ratio of such 35 ammonium groups : remaining (meth)acrylic esters of 1 :  $\geq 10$ , for example around 1 : 20 or 1 : 40, and with a mean molecular weight of around 150000. Such polymers correspond to USP/NF 2 "Ammonio methacrylate copolymers, Type A and Type B".

Further suitable generic classes and specific examples of pharmaceutically acceptable methacrylic acid copolymer are known polymers which are copolymers, anionic in character, based on methacrylic acid and methyl methacrylate, for example having a ratio of free carboxyl groups : methyl-esterified carboxyl groups of 1 : >3, e.g. around 1 : 1 or 1 : 2, and with a mean molecular weight of 135000.

Such polymers are sold under the trade name Eudragit™, such as the Eudragit L series e.g. Eudragit L 12.5™, Eudragit L 12.5P™, Eudragit L100™, Eudragit L 100-55™, Eudragit L-30™, Eudragit L-30 D-55™, the Eudragit S™ series e.g. Eudragit S 12.5, Eudragit S 12.5P™, Eudragit S100™, the Eudragit NE™ series e.g. Eudragit NE 30D™, the Eudragit RL™ series, e.g. Eudragit RL 12.5™, Eudragit RL 100™, Eudragit RL PO™, Eudragit RL 30D™, and the Eudragit RS™ series e.g. Eudragit RS 12.5™, Eudragit RS 100™, Eudragit RS PO™, and Eudragit RS 30D™. Some of these polymers are known enteric polymers (the term "enteric polymer" is a term of the art referring to a polymer which is preferentially soluble in the less acid environment of the intestine relative to the more acid environment of the stomach), for example having a solubility in aqueous media at pH 5.5 and above. These Eudragit polymers may be used either alone or with a plasticiser.

The coating may be applied using either an aqueous medium or a non-aqueous medium such as an organic liquid, for example a methanol: methylene dichloride mixture. A non-aqueous medium may be more suitable if the active ingredient comprises or contains a clavulanate salt. The choice of plasticiser will depend upon whether an aqueous or non-aqueous medium is used, for example suitable plasticisers for an aqueous medium include propylene glycol, triethyl citrate or acetyl triethyl citrate, and for a non-aqueous medium include these and also dibutyl or diethyl phthalate. The coating may also include an anti-tack agent such as talc or silica. The enteric coating may be applied using an essentially conventional method, for example dissolving or suspending the enteric coating material in the medium, then spraying the solution or suspension onto the granules, followed by drying and screening.

The granules of this invention may be made up into pharmaceutical formulations in a conventional manner, e.g. by packing into sachets or other containers, or by tabletting, e.g. by a conventional process of compaction to provide a tablet formulation. The invention therefore also provides a tablet which includes the above-described granules.

The invention also provides a process for the use of a granule as described above in the manufacture of a medicament for the treatment of bacterial infections.

5 The invention also provides a method of treatment of bacterial infections in humans and animals which comprises the administration of a therapeutically effective amount of granules as described above.

The invention also provides pharmaceutical granules as described above for use in the treatment of bacterial infections.

The following examples illustrate the invention.

10

<u>Example 1</u>	<u>mg/dose</u>
Amoxycillin trihydrate	300 f.a.
Colloidal silica	1.8
Sodium lauryl sulphate	3.6
Kollidon 25 (polyvinylpyrrolidone)	5.4
Eudragit L100	14.0
Propylene glycol	1.4) Solids from
Aerosil 200	1.0) Enteric coat

The first four ingredients were granulated using water and then enteric coated using methylene dichloride/methanol (60/40 v/v).

15

<u>Example 2</u>	<u>mg/dose</u>
Potassium clavulanate	150 f.a.
Pharmacoat 603	9
Colloidal silica	3.4
Glycine	22.5
Sodium lauryl sulphate	2.3
Eudragit L100	152.1)
Diethyl phthalate	19.1) Solids from
Talc	22.8) Enteric coat

20 The first four ingredients were granulated using methylene dichloride/methanol (70/30 v/v). and then enteric coated using methanol/methylene dichloride (40/60 v/v).

<b>Example 3</b>	<b>mg/dose</b>
Potassium clavulanate	1002.0g.
Pharmacoat 603	48.0g
Colloidal silica	18.0g
Glycine	120.0g
Sodium lauryl sulphate	12.0g

**Granulating mixture:**

Isopropyl alcohol	300ml
Methylene dichloride	700ml
Eudragit L100	334g
Diethyl phthalate	42g
Talc	50g
Methanol	2000ml
Methylene dichloride	3000ml

**5 Process**

- Screen the potassium clavulanate 16 mesh. Screen the Aerosil and Pharmacoat 20 mesh. Blend all ingredients in a planetary mixer for 5 minutes, then granulate with the granulating mixture. (The above weights of solid ingredients require approximately 460ml. of granulating mixture.) Extrude the granules through a 1mm. aperture and marumerise, wetting the particles slightly with granulating mixture as necessary. Dry the marums in a fluid bed dryer for 45 minutes at 45°C. Screen the marums, retaining those between 12 and 30 mesh. Prepare the coating solution by dispersing the Eudragit in the methylene dichloride using a high speed mixer. Add the methanol and stir until the solution clears. Add the diethylphthalate and talc. Stir for 15 minutes. Load the marums into a coating pan and warm for at least 15 minutes. Spray the coating solution on the tumbling marum bed at about 25 ml/min. 15 litres of solution was sprayed on to 2100 g. of marums. Screen the dried, coated marums.

**20 Example 4**

Amoxycillin trihydrate	4900g
Colloidal silica (Aerosil 200)	25g
Sodium lauryl sulphate	50g

**Granulating solution**

Polyvinylpyrrolidone (Kollidon 25, Trade Mark)	75g
Water	1463g

**Coating solution**

Eudragit L100 (Trade Mark)	200g
Colloidal silica	15g
Propylene glycol	20g
Dichloromethane	1800g
Methanol	1200g

**5 Process**

- Blend the amoxycillin trihydrate, colloidal silica and sodium lauryl sulphate in a planetary blender. This is wet massed with the granulating solution, and the resulting granules are extruded at medium speed on a (EXKS-1) extruder fitted with a 0.7 mm screen. The extrude is then spheronised at fast speed on the Marumeriser, allowing a residence time for extrudates of 1-2 minutes. Marums are dried in a fluid bed drier for 2 hours at 60°C in divided lots of 2-3kg. These are subsequently blended and the fraction <14#>30# retained.
- 10

**Coating**

- 15 The constituents of the coating suspension are mixed until uniform. The vessel of a fluidised bed coater previously fitted with a spray gun for co-current application is loaded with 1kg granules. The bed is warmed for a few minutes with warm inlet air. Spray the coating suspension until sufficient coat is applied.

**20 Example 5**

1	Potassium clavulanate	1002.0g
2	Pharmacoat 603	48.0g
3	Colloidal silica	18.0g
4	Glycine	120.0g
5	Sodium lauryl sulphate	12.0g

**Granulating solution**

6	Isopropyl alcohol	300ml
7	Methylene dichloride	700ml

**Coating suspension**

		% w/w
8	Eudragit L300	52.2
9	Citroflex A2 (acetyltriethylcitrate) (equivalent to 10% dry lacquer)	1.6
10	Talc	7.8
11	Water	38.4

**Process**

- Screen the potassium clavulanate through 16 mesh screen.
- 5 Screen the colloidal silica and Pharmacoat through 20 mesh screen  
Blend all the ingredients in a planetary mixer for 5 minutes, then granulate with the granulating solution. (The weights above require approximately 460ml of solution). Extrude the granules through a 1mm aperture and marumerise, wetting the particles slightly with granulating solution as necessary.
- 10 Dry the marums in a fluid bed drier for 45 minutes at 40°C.  
Screen the marums, retaining those between 12 and 30 mesh.

**Coating**

- 15 The constituents of the coating suspension are mixed until uniform using a high shear mixer (e.g. Silverson).

The vessel of a fluid bed granulator, having previously been fitted with a spray gun for co-current application, is loaded with an appropriate weight of marums.

- 20 The bed of marums is warmed for 5 minutes at an air inlet temperature of 40°C.  
The coating suspension is sprayed at a flow rate of approximately 3 to 4 L per minute at an atomising pressure of 0.2 bar. Sufficient coat is applied so that the coated marums meet the following dissolution requirements. The clavulanate is essentially not released at pH 2 and 4 (preferably less than 10% of the clavulanate content being released of this pH), and achieve almost total release (greater than 80%, and preferably greater than 90%) by the end of the test at pH 7.

Note: approximately 400g of coating suspension (= 63g of solids) is needed for each 100g of marums.

- 25 The coated marums are dried for 10-15 minutes at 40°C.  
The dried, coated marums are screened and those between 10 and 12 mesh are retained.

**Claims:**

1. A pharmaceutical granule, comprising: an active ingredient which comprises one or more beta-lactam antibiotics and/or one or more beta-lactamase inhibitors; and one or more surfactants which are Group I or Group II metal (C<sub>10</sub>-17) alkyl sulphates.
2. A pharmaceutical granule according to claim 1 characterised in that the antibiotic is selected from amoxycillin and ampicillin, and the beta-lactamase inhibitor is a salt of clavulanic acid.
3. A pharmaceutical granule according to claim 2 characterised in that the beta-lactamase inhibitor is potassium clavulanate and the antibiotic is amoxycillin.
4. A pharmaceutical granule according to any one of claims 1 to 3 characterised in that the surfactant(s) is a sodium alkyl sulphate.
5. A pharmaceutical granule according to claim 4 characterised in that the surfactant is sodium lauryl sulphate.
6. A pharmaceutical granule according to any one of claims 2 to 5 characterised in that the granule also contains an amino acid.
7. A pharmaceutical granule according to any one of claims 1 to 6 characterised in that the relative proportions of the components in the granule are: antibiotic, beta-lactamase inhibitors or combination thereof: 50 wt. % or more; surfactant: 0.5 - 5 wt. %; granulating aid: 0 - 7.5 wt. %; fillers/spheronising aids 0 - 25 wt. % expressed as total granule weight.
8. A pharmaceutical granule according to any one of claims 1 to 7 coated with a coating which may be an at least partly water-resistant.
9. A process for the manufacture of a pharmaceutical granule, comprising admixing one or more beta-lactam antibiotics, and/or one or more beta-lactamase inhibitors with one or more surfactants which are Group I or Group II metal (C<sub>10</sub>-17) alkyl sulphates, and then granulating the mixture.

10. A process wherein a granule according to any one of claims 1 to 7 is coated with an at least partly water resistant coating.
11. A pharmaceutical tablet which includes granules according to any one of 5 claims 1 to 8.
12. A process characterised in that granules according to any one of claims 1 to 8 are compacted into a pharmaceutical tablet.
- 10 13. A process for the use of a granule according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment of bacterial infections.
14. A method of treatment of bacterial infections in humans and animals 15 which comprises the administration of a therapeutically effective amount of granules according to any one of claims 1 to 8.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 95/01039

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/43 A61K9/16 A61K47/20

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 293 975 (AKZO N.V.) 7 December 1988 see example 7 ---	1-7,9, 13,14
X	US,A,4 602 012 (GORDON G. WEINGARTEN) 22 July 1986 see column 31 ---	1,4,5,7, 9,11-14
X	FR,A,2 523 446 (DIETLIN, FRANCOIS) 23 September 1983 see page 3, paragraph 4 - page 4, line 32 see examples I-IV ---	1-5,11, 12
Y	EP,A,0 411 952 (MCNEILL-PPC INC) 6 February 1991 see page 2, line 10 - page 3, line 53 ---	1-14
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

'&' document member of the same patent family

1

Date of the actual completion of the international search

12 June 1995

Date of mailing of the international search report

03.07.95

## Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+ 31-70) 340-3016

## Authorized officer

Tzschoppe, D

**INTERNATIONAL SEARCH REPORT**Int'l Application No  
PCT/EP 95/01039

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,91 16893 (BEECHAM GROUP PLC) 14 November 1991 see page 1 - page 2 -----	1-14

1

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No  
PCT/EP 95/01039

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-293975	07-12-88	AU-B-	607784	14-03-91
		AU-A-	1932088	21-12-88
		WO-A-	8809173	01-12-88
		JP-T-	2500591	01-03-90
US-A-4602012	22-07-86	AT-B-	392279	25-02-91
		AT-A-	1790	15-11-93
		AT-B-	392073	25-01-91
		AU-B-	578441	27-10-88
		AU-A-	3704684	11-07-85
		BE-A-	901436	03-07-85
		CA-A-	1265512	06-02-90
		CH-A-	666274	15-07-88
		DE-A,C	3500090	11-07-85
		FR-A,B	2557571	05-07-85
		GB-A,B	2152504	07-08-85
		JP-A-	60172989	06-09-85
		LU-A-	85719	22-10-85
		NL-A-	8403974	01-08-85
		SE-B-	466451	17-02-92
		SE-A-	8500011	04-07-85
FR-A-2523446	23-09-83	NONE		
EP-A-411952	06-02-91	AU-B-	646399	24-02-94
		AU-A-	6018190	07-02-91
		CA-A-	2022640	05-02-91
		GR-B-	1001171	07-06-93
		US-A-	5320855	14-06-94
		US-A-	5215755	01-06-93
WO-A-9116893	14-11-91	AU-B-	657476	16-03-95
		AU-A-	7778391	27-11-91
		EP-A-	0528846	03-03-93